DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Jaya Ayyagari
Senior Manager, Regulatory Affairs
Dr. Reddy's Laboratories, Inc.
200 Somerset Corporate Blvd., 7th Floor
Bridgewater, NJ 08807

RE: ANDA 91316
Fondaparinux Sodium Solution for subcutaneous injection
MA #2

Dear Mr. Ayyagari:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the healthcare professional (HCP) Product Information Website (website or webpage)[1] for Fondaparinux Sodium Solution for subcutaneous injection (fondaparinux sodium) submitted by Dr. Reddy's Laboratories, Inc. (Dr. Reddy's) under cover of Form FDA-2253. The website is false or misleading because it minimizes important risk information associated with the drug in violation of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 352(a) & (n). *See* 21 CFR 202.1(e)(7)(viii).

Background

Below are the indication and summary of the most serious and common risks associated with the use of fondaparinux sodium.[2] According to its FDA-approved product labeling (PI), fondaparinux sodium is indicated for the following:

> Fondaparinux sodium injection is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):
>
> - in patients undergoing hip fracture surgery, including extended prophylaxis;
> - in patients undergoing hip replacement surgery;
> - in patients undergoing knee replacement surgery;
> - in patients undergoing abdominal surgery who are at risk for thromboembolic complications.
>
> . . . Fondaparinux sodium injection is indicated for the treatment of acute deep vein thrombosis when administered in conjunction with warfarin sodium.

[1] Fondaparinux website, http://csd.bodhtree.co.in/drreddys/fonda/v2/hcp/ (last accessed, December 22, 2011).
[2] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

> . . . Fondaparinux sodium injection is indicated for the treatment of acute pulmonary embolism when administered in conjunction with warfarin sodium when initial therapy is administered in the hospital.

Fondaparinux sodium is associated with several risks. The Boxed Warning section of the PI states the following (emphasis in original):

> **WARNING: SPINAL/EPIDURAL HEMATOMAS**
> Epidural or spinal hematomas may occur in patients who are anticoagulated with low molecular weight heparins (LMWH), heparinoids, or fondaparinux sodium and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:
>
> - use of indwelling epidural catheters
> - concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants
> - a history of traumatic or repeated epidural or spinal puncture
> - a history of spinal deformity or spinal surgery
>
> Monitor patients frequently for signs and symptoms of neurologic impairment. If neurologic compromise is noted, urgent treatment is necessary.
>
> Consider the benefit and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis. . . .

Fondaparinux sodium is contraindicated in the following conditions: severe renal impairment, active major bleeding, bacterial endocarditis, thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of fondaparinux sodium, and body weight <50 kg (venous thromboembolism (VTE) prophylaxis only). Furthermore, according to the WARNINGS AND PRECAUTIONS section of the PI, fondaparinux sodium should be used with extreme caution in conditions with increased risk of hemorrhage, such as congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, uncontrolled arterial hypertension, diabetic retinopathy, or shortly after brain, spinal, or ophthalmological surgery. The PI also contains the following Warnings and Precautions: fondaparinux sodium increases the risk of bleeding in patients with impaired renal function and increases the risk for bleeding in patients who weigh less than 50 kg. In addition, thrombocytopenia can occur with the administration of fondaparinux sodium. Other Warnings and Precautions include neuraxial anesthesia and post-operative indwelling epidural catheter use, and monitoring of laboratory tests.

The most common adverse reactions associated with the use of fondaparinux sodium were bleeding complications.

Minimization of Risk Information

The HCP promotional website minimizes the serious risks associated with fondaparinux sodium by failing to prominently display the Boxed Warning for this drug. Specifically, the HCP website presents effectiveness claims for fondaparinux sodium at the top portion of the webpage, followed by what appears to be a direct reprint of the fondaparinux sodium PI that starts with the Indications & Usage section, followed by the Dosage & Administration section, and so forth. However, the Boxed Warning, which describes the very serious risk of epidural or spinal hematomas, is not presented until the bottom of the webpage, after sections such as "How Supplied" and "Patient Advice." Additionally, the navigation tab on the left-hand side of the webpage appears to list all of the sections in the PI. However, upon further inspection the Boxed Warning section is not included on the navigation tab. Presenting the Boxed Warning in this manner, where it is unlikely to draw the viewer's attention, minimizes the serious and significant risk of long term or permanent paralysis from spinal or epidural hematomas. While this risk is conveyed as part the patient video and text at the very bottom of the website, the overall effect of this presentation undermines the communication of the Boxed Warning regarding the risk of spinal/epidural hematomas and potential paralysis, misleadingly suggesting that the drug is much safer than has been demonstrated by substantial evidence.

Conclusion and Requested Action

For the reasons discussed above, the website misbrands fondaparinux sodium in violation of the FD&C Act, 21 U.S.C. 352(a) & (n). *See* 21 CFR 202.1(e)(7)(viii).

OPDP requests that Dr. Reddy's immediately cease the dissemination of violative promotional materials for fondaparinux sodium such as those described above. Please submit a written response to this letter on or before January 10, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for fondaparinux that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned by facsimile at (301) 847-8444, or at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Promotion (DPP) and the Division of Direct-to-Consumer Promotion (DDTCP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to the MA # in addition to the ANDA number in all future correspondence relating to this particular matter. DPP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for fondaparinux sodium comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

James S. Dvorsky, PharmD
Regulatory Review Officer
Division of Professional Promotion
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES S DVORSKY
12/22/2011